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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/993,363
Filing Date: November 14, 2001
Appellant(s): ASHTON-RICKARDT ET AL.

Mark B. Wilson, FULBRIGHT & JAWORSKI L.L.P.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 08-13-04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 26-35, 37-40, 42-44, 48-50, and 61-74 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Clay et al. Pathology Oncology Research 5:3-15, 1999.

Romano et al. Stem Cells 2000; 18:19-39.

Tan et al. Blood 93:1506-1510, 1999.

McMichael et al. Nature 410:980-987, 2001

Bordie et al. Nature Medicine 5:34-41, 1999.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(i) Claims 26-35, 37, 42-44, 48-50, 61-65, 67, and 71-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claimed invention encompasses a method that comprises an expression construct comprising a DNA segment that encodes a serpin or serpin mimetic under the control of a promoter active in a cytotoxic-T-lymphocyte. Dependent claims limit the serpin or serpin mimetic to an inhibitor of granzyme activity, granzyme transcription, granzyme translation, and a serpin or serpin mimetic that increases granzyme degradation or destabilizes granzyme. However, the specification does not provide sufficient written description support for the claimed genus of serpin or serpin mimetic.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. When the claims are analyzed in light of the

specification, instant invention recites a genus, a serpin or serpin mimetic. However, the specification does not teach what is the complete structure of representative number of species of the genus and what is the core structure required for the members of the genus. It is noted that the term serpin is broadly used for any endogenous serine protease inhibitor. Applicants' listing of SP16, P19, P-6, MNEI, PI-8 and PAI-2 as serpins does not provide sufficient description for the entire genus because their structure is not representative of the entire genus. Additionally, because, all these serpins inhibit the enzyme activity of serine protease and none of these inhibit the transcription, translation, or increase degradation as recited, for example, in claims 34 and 64, they represent members of only one subgenus, which inhibit enzyme activity. Furthermore, the specification does not teach what is the common required structure even for this subgenus. It is noted that serpins that inhibit transcription, translation, or increase degradation as recited noted that each of these will represent a subgenus because it's members will have a function different from the function of the members of another subgenus. There is no description in the specification if there is a core structure that would be common to all the members of the claimed genus. The specification does not teach what would be the core structure or complete structure of sufficient number of species of each subgenus. Yet another subgenus of the claimed invention is serpin mimetic. A mimetic is a synthetic molecule that is an analog of a natural material. Thus a serpin mimetic will be a synthetic analog of a serpin. The specification does not teach the structure of any serpin mimetic. While an artisan could interpret a serpin mimetic to have serpin function, an artisan would not know what is the structure of the mimetic. It is emphasized that as discussed for serpins, the claimed invention encompasses serpin mimetics that inhibit the transcription, translation or activity, or increase degradation of a serine protease. The specification does not teach the core structure or complete structure for any of these subgenera.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would

distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the serpin inhibits activity, transcription, or translation of granzyme or it increases degradation of granzyme or destabilizes granzyme. The specification does not disclose any identifying characteristic as to how an artisan would have differentiated or identified different inhibitors and species of the genus or subgenus. Again, the members of any of these subgenera themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenera. Additionally, the specification does not teach the relevant identifying characteristics of serpin mimetics that inhibit the transcription, translation or activity, or increase degradation of a serine protease.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of serpins or serpin mimetics at the time the application was filed. Thus it is concluded that the specification does not meet the written description requirements.

(ii) Claims 26-35, 37-40, 42-44, 48-50, and 61-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention is drawn to a method of inducing immunity or enhancing immunity in any subject with any viral infection with any granzyme inhibitor wherein the subject is either administered an expression vector or cytotoxic T-lymphocytes comprising the expression vector. However, the specification as filed does not provide sufficient guidance for an artisan of skill to make and use the claimed invention and an artisan of skill would have required undue experimentation to practice the claimed invention because the art of gene therapy or therapy of a viral infection with CTLs is unpredictable and the specification does

not provide any guidance as to how to address the issues of unpredictability in the art. It is noted that the HIV and PI9 have been elected as species for prosecution and the specification does not teach how to induce immunity in a HIV infected subject or any subject with any viral infection by the claimed method.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification as filed teaches general teachings of making vectors, expression system, viral vectors etc. The specification also reviews the role of serpins in apoptosis regulation. The specification also teaches vector for expressing SPI6 and PI-9. The specification teaches working example of in vitro effect of SPI6 on viability and function of CTLS (see the working examples). The specification also teaches a transgenic mouse over expressing SPIS wherein the human CD2 promoter directs the expression of SPI6 in NK cells, mature T cells and thymocytes (see example 3). However, the specification does not teach any effect of either SPI6 or PI-9 or any other granzyme inhibitor on immunity in vivo in any disease

model. It is noted that the SPI6 mouse is not an art-recognized model for any disease or for HIV.

The claimed invention is not enabled by the instant specification because the art of gene therapy and of cell therapy using CTLs is unpredictable as recognized in the art. Clay et al (Pathology Oncology Research 5:3-15, 1999) look at the some of the technical and biological hurdles that need to be addressed in gene therapy trials and conclude, "Unfortunately, no gene therapy trial to date has been conclusively proven to be effective in treating the targeted disease.....It is clear that greater emphasis should be placed in vector development and understanding the biology of gene therapy targets if we expect gene therapy to be a viable option in the future..... Further advances will also be required in vector development and in establishing the optimum transduction conditions for target cells to enhance the efficiency of gene transfer and to provide prolonged gene expression."

Romano et al (Romano et al. Stem Cells 2000; 18:19-39) reporting on the recent developments of gene therapy, noted," However, the real effectiveness of gene therapy programs is still in question. After a decade of clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage."

It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy protocols and applications where the mechanism of action and some efficacy has been determined in animal models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. Even with such results, it is uncertain whether there would be a therapeutic effect when the studies obtained in a mouse model or another animals model is extended to a human subject.

In particular, in case of claims 26-29, claims encompass administration of the expression vector by any route and then the vector has to reach CTLs and expressed in there. However, the specification does not teach as to how the DNA administered by any route will be directed to CTLs such that sufficient amount of inhibitor peptide is produced. While the claims reciting using a promoter specific to CTLs, there is no evidence and direction as to how the expression vector will reach

the CTLs in the first place and in sufficient amounts. It is noted that the specification has used a SPI6 expressing transgenic mouse, which was infected with LCMV. However, this is not a natural animal model because there is no issue of gene delivery to cells since the mouse has the transgene in all of its cells, however, a subject can not be made transgenic for a transgene such as SPI6 and therefore, one can not predict whether the gene of interest can reach the target cells in sufficient amounts. The specification does not provide any guidance regarding this. Additionally, the claimed invention encompasses any inhibitor, again the specification does not teach as to how any inhibitor will be expressed and the method practiced.

Next, claims 30-35, 37-40, 42-44, 48-50 and 61-74 50 encompass CTLs derived from any source and administered to any subject which will included CTLs of autologous, allogeneic or xenogeneic origin or from any subject with any disease or condition and administered to any subject with any disease or condition. It is debated in the art whether CTLs can be effectively used in treating HIV. For example, Bordie et al Nature Medicine 5:34-41, 1999), while reviewing the state of the art of HIV-1 specific CTLs noted that while primary infection is associated with a vigorous CTL response, HIV-specific CTLs seem to be primarily localized to blood rather than lymph nodes (see second paragraph in the left column on page 34). Another limitation of the method they argue is that the in vivo activity of the transferred CTLS cannot be assessed as persistence was limited by the induction of a host CTL response to foreign proteins, such as to HSV Tk or hygromycine phosphotransferase used for selecting cells in culture. It is emphasized that the specification does not teach how to specifically teach inducing or enhancing immunity in a subject against HIV. In fact there are only two references to HIV in the specification, one on page 2, lines 17-24 and page 8, lines 13 and none of these sections provide any specific teaching as to how an artisan have practiced in a subject with HIV infection. Tan et al (Blood 93:1506-1510, 1999) in their study on the death of adoptively transferred T cells in AIDS, noted, "Because trials of adoptive cell transfer in HIV are laborious and infrequent, the generality of these findings will need to be confirmed by different groups. Subsequent trials should

take into account the vulnerability of cells culture in vitro to apoptosis and use means for quantifying their survival in vivo. Engineering apoptosis-resistant antigen specific CTL may circumvent the obstacle, but the success of this strategy depends on better elucidating the mechanism of cell death in vivo". The specification does not address the issue of cell culture and how the cells will be quantified in vivo and what will be the fate of the cells in vivo. In yet another review article, McMichael et al (Nature 410:980-987, 2001) reviewed the state of the art of the complexity of cellular response to HIV and noted that it was not clear what functions of CTLs are most important for controlling HIV and that knockout mice for Perforin while do not recover from LCMV infection, these mice handle other viral infections effectively which indicates that the granzyme and perforin mediated cell lysis may not be mechanistically same in all the viral infections (see page 981, right column). In other words, one would not expect to see same type of effect of granzyme inhibitor on immunity for any virus. Therefore, one will question whether the results disclosed in the specification are applicable to HIV or any other virus.

It is noted that claims 31-33 and 61-63 recite different viral vectors, however, the specification except for providing general description of vectors, does not provide any specific details. It is noted that it is recognized in the art that vectors are one of the major limitations of a method of gene therapy. As noted by Clay et al, "It is clear that greater emphasis should be placed in vector development and understanding the biology of gene therapy targets if we expect gene therapy to be a viable option in the future..... Further advances will also be required in vector development and in establishing the optimum transduction conditions for target cells to enhance the efficiency of gene transfer and to provide prolonged gene expression."

Claim 34 recites inhibitors that inhibit anything from granzyme activity to transcription, translation etc., however, the specification does not teach how to make all these inhibitors and administer them to a subject either as expression vector or as a cell comprising the expression vector so as to effect enhancement or induction of immunity. The specification does not teach the nucleotide sequence encoding any inhibitor of granzyme transcription, translation or other recited

functions. Regarding claims 48-50, it is noted that in view of the unpredictability issues discussed above, an artisan would not have been able to increase number of CTLs or augment CTL function or augment memory cell development.

In conclusion, the art of gene therapy and CTL therapy is highly unpredictable in general. Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. The courts have stated that reasonable correlation must exist between scope of a right to exclude a patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of any viral function and by any route of administration as broadly claimed, the lack of direction or guidance provided by the specification was well as the absence of working examples with regard to a therapeutic effect, it would have required undue experimentation of one skilled in the art to use the claimed invention as broadly claimed.

(11) Response to Argument

(i) Response to Arguments- Written Description Rejection

Applicant's arguments filed 08-13-04 have been fully considered but they are not persuasive. Applicants' point to different parts of the specification for providing written description support for the claimed invention. For example, on page 10 of the brief, the second full paragraph of the brief states:

> The Specification clearly discloses a representative number of species of the genus "serpin and serpin mimetics." See Specification, page 4, lines 20-26; page 5, lines 21-23; page 15, lines 15-16; Page 15, line 21 through page 16, line 4; Page 19, lines 12-14; Page 37, lines 22-24. In particular, a review article pertaining to serpins is cited on page 4, line 21 of the Specification. Examples of particular serpins useful in the context of the invention are cited in the Specification, and include SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, and plasminogen activator inhibitor (PAI-2). Specification, page 6, lines 21-24. Further,

However, except for listing SPI6, PI9, PI-6, MNEI, PI-8 and PAI-2, which are all serpins that inhibit the activity of granzyme (a serine protease), the indicated sections of the specification describe neither the full structure nor relevant identifying characteristics of representative serpins that inhibit transcription or translation of granzymes or that increase degradation or destabilization of granzyme. Additionally none of the indicated parts of the specification describe the full structure or relevant identifying characteristics of serpin mimetics that inhibit activity, transcription or translation or granzymes or that increase degradation or destabilization of granzyme. Applicants cite *In re Gosteli, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989)* and *Lockwood v. American Airlines, Inc., 107 F.3d 1565,1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997).* However, the instant specification does not meet the written description criteria as discussed in these two case laws since the specification as filed does not describe any serpin that inhibits transcription or translation of granzymes or that increase degradation or destabilization of granzyme or any serpin mimetic that inhibits activity, transcription or translation or granzymes or that increase degradation or destabilization of granzyme, by descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention and therefore, the description as filed does not allow(s) persons of ordinary skill in the art to recognize that he or she invented what is claimed.

Applicants argue that by describing PI9, they have described a large number of representative members of the genus of serpins and serpin mimetics, however, they fail to recognize that PI9 and likes of serpins, that the specification has

described, only inhibit granzyme activity and that there is no description of serpin or serpin mimetics that inhibit transcription or translation or increase degradation or destabilization. Applicants arguments *"The Examiner, in his response, appears to be arguing that Appellants must prove that each and every serpin or serpin mimetic encompassed by the claimed invention must be shown to enhance or induce immunity to a viral infection and inhibit granzyme function or activity by any mechanism"* are misplaced and erroneous because no such requirement has been placed rather a simple interpretation of the written description requirement has been applied which requires description of a sufficient number of representative species of a genus claimed. It is emphasized that the genus claimed in the instant instance is enormous and diverse and comprises multiple subgenera that would not share the same common structure and will have different function (as claimed) as well.

Applicants' arguments that examiner interpreted laws of written description erroneously by arguing *"The sections of the specification referred to by the applicants in their response do not describe representative number of species of serpin or serpin mimetics that would enhance or induce immunity to any viral infection and that would inhibit granzyme function or activity by any mechanisms"* (see last paragraph on page 12 of the response) do not correct the deficiency of the specification that lacks written description for the claimed invention. Instant specification does not satisfy the Vas-cath case law because the Specification did not describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention.

Applicants' arguments that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed (In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)) and that PTO has not met the initial burden of presenting the evidence or reasons is not persuasive and is misplaced because the office action has provided reasoning as to how the claimed invention is a genus comprising diverse subgenera that have

diverse functions and the members of genera will have diverse structure and function. Therefore, the office has met its burden.

Applicants argue that subject matter of claims 34, 35, 64, and 65 meets the written description requirement because they contain additional function, however, as discussed above because of different functions the serpins will belong to different subgenera. Likewise, applicants' arguments, that claims 37 and 67 meet the written description requirement because they recite a serpin, are not persuasive since serpin is the genus and as discussed above the specification does not describe sufficient number of species of the genus and subgenera claimed.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of serpins or serpin mimetics at the time the application was filed. Thus it is concluded that the specification does not meet the written description requirements.

(ii) Response to Arguments-Enablement Rejection

Applicant's arguments filed 08-13-2004 have been fully considered but they are not persuasive. Applicants have argued that the office action of March 19 2003 indicated that the declaration was persuasive to establish that LCMV infection in humans. At the onset, the examiner would like to clarify this statement because the examiner only meant that some of the characteristics of LCMV infection resemble HIV infection. It is noted that none of the arts discussed in the declaration by itself discussed that the LCMV infection had all the characteristics of the HIV infection and in fact there is no such article in the state of the art of HIV that indicates that LCMV infection is an art recognized model of HIV infection. Therefore, while the declaration establishes that LCMV infection has some resemblance to HIV infection, it is not an art-recognized model of HIV infection.

Applicants argue that the specification provides substantial amount of information pertaining to enhancing or inducing immunity to a viral infection, For

example, applicants refer to page 2, lines 17-23, page 1, line 1 through page 5, line 17; page 13 line 20 through page 14, line 24, page 14, line 27-page 16, line 4. However, all these sections of the specifications referred to by the applicants are general statements and do not provide any specific information as to how the method of enhancing or inducing immunity to any viral infection, in particular HIV will be practiced by providing an expression vector encoding a serpin or serpin mimetic. Applicants argue that the declaration established that one of ordinary skill in the art would be able to make and use the claimed invention without undue invention, however, these arguments are not persuasive because the declaration does not provide any factual evidence to address the enablement issues, unpredictability of the state of the art and lack of specific guidance for practicing the claimed method. Except for comparing the discussion in different articles and reiterating what was argued by the applicants' representative, the declaration did not address the issues of enablement: unpredictability of the state of the art of gene therapy and CTL therapy, unpredictability of the route of administration and unpredictability whether sufficient amount of serpin or serpin mimetic could be produced that would be sufficient to produce therapeutic effect, unpredictability of the state of CTL transplantation from any donor to any recipient, lack of any specific guidance for treating HIV infection (particularly in view of the complexity of cellular response in HIV infection) or any viral infection in general. It is noted that all these issues are specific issues and would require specific and extensive guidance, which is missing in the specification or declaration or arguments by the applicants. It is emphasized that mere arguments cannot replace factual evidence.

On page 19 applicants argue that the working examples address treatment of viral disease, particularly example that demonstrates effect of SPI6 on the LCMV-infected mouse. However, as discussed above, a transgenic mouse expressing a therapeutic protein could not be a model for gene therapy because while it could show effect of the protein, it could not teach how to deliver sufficient amount of the gene therapy vector that would express sufficient amount of therapeutic protein that would be effective to treat an infection. A transgenic animal does not address the issue of vector delivery to a cell in vivo. Likewise a transgenic animal does not

address the issue of CTL transplantation. Applicants seem to have ignored all these unpredictability issues and did not address as to how their specification or transgenic animal address these issues critical for gene therapy or cell therapy.

Pages 20-22 continued on page 23 of the applicants' arguments are directed to Dr. Welsh's declaration, that he is an expert and that his declaration by discussing parts of the specification and certain research articles shows that by following the teachings of the specification an artisan would be able to practice the claimed invention, however, like the specification, Dr. Welsh's declaration does not provide any specific teaching rater reiterates the same general information as present in the specification. No factual evidence was presented in the declaration.

Page 23-24 of the response argues that the art of gene therapy and cell therapy are not so unpredictable and cite the abstract of the article which discusses the clinical trials and growth and development in the field of gene therapy and that gene therapy and cell therapy using CTLs is not inoperable. First, the abstract of the Romano article does not in any way indicate that gene therapy methods were routine in 2000 and applicants have not presented any evidence that indicated that by the filing date of their application the art had become routine. Second, the office action did not indicate that gene therapy and cell therapy using CTLs was inoperable, rather that they were not routine. Based on the state of the art of gene therapy at the time of the invention, there was no one vector or method that could be applied to any condition.

Applicants argue that claims 42-44 and 71-73 were patentable over other claims because they recite specific viruses. However, these arguments do not remedy the deficiency of the specification does not teach any specific guidance for treating any disease and also other issues discussed in the enablement rejection are not addressed by this argument.

In conclusion, the art of gene therapy and CTL therapy is highly unpredictable in general. Thus, the cited prior and post-filing art clearly indicates an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect,

gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of any viral function and by any route of administration as broadly claimed, the lack of direction or guidance provided by the specification was well as the absence of working examples with regard to a therapeutic effect, it would have required undue experimentation of one skilled in the art to use the claimed invention as broadly claimed.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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